



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Abacavir (ABC, Ziagen) (Last updated April 14, 2020; last reviewed April 14, 2020)

### Formulations

**Pediatric Oral Solution:** 20 mg/mL

**Tablet:** 300 mg (scored)

#### Generic Formulations:

- 300 mg tablet
- 20 mg/mL pediatric oral solution

#### Fixed-Dose Combination Tablets:

- [Epzicom and generic] Abacavir 600 mg/lamivudine 300 mg
- [Triumeq] Abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg
- [Trizivir and generic] Abacavir 300 mg/lamivudine 150 mg/zidovudine 300 mg

When using fixed-dose combination (FDC) tablets, refer to other sections of the [Drug Appendix](#) for information about the individual components of the FDC. See also [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents](#).

For additional information, see [Drugs@FDA](#) or [DailyMed](#).

### Dosing Recommendations

#### Neonate and Infant Dose:

- Abacavir (ABC) is not approved for use in infants aged <3 months

#### Infant and Child (Aged ≥3 Months) Dose

##### Oral Solution:

- ABC 8 mg/kg twice daily (maximum 300 mg per dose) or ABC 16 mg/kg once daily (maximum 600 mg per dose)
- In infants and young children who are being treated with liquid formulations of ABC, initiation with once-daily ABC is not generally recommended. In older children who can be treated with tablet formulations, therapy can be initiated with once-daily administration. In clinically stable patients who have undetectable viral loads and stable CD4 T lymphocyte cell counts while receiving the liquid formulation of ABC twice daily, the ABC dose can be changed from twice-daily dosing to once-daily dosing with the liquid or tablet formulations (see text below).

### Selected Adverse Events

- Hypersensitivity reactions (HSRs) can be fatal. HSRs usually occur during the first few weeks of starting therapy. Symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms (e.g., cough, shortness of breath).

### Special Instructions

- Test patients for the HLA-B\*5701 allele before starting therapy to predict the risk of HSRs. Patients who test positive for the HLA-B\*5701 allele should not be given ABC. Patients with no prior HLA-B\*5701 testing who are tolerating ABC do not need to be tested.
- Warn patients and caregivers about the risk of serious, potentially fatal HSRs. Occurrence of an HSR requires **immediate and permanent discontinuation of ABC. Do not rechallenge.**
- ABC can be given without regard to food. The oral solution does not require refrigeration.
- Screen patients for hepatitis B virus (HBV) infection before using Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets). These FDC tablets contain lamivudine (3TC), and severe acute

### Weight-Band Dosing for Children and Adolescents Weighing $\geq 14$ kg

Weight	Scored 300-mg Tablet		
	Twice-Daily Dose, AM	Twice-Daily Dose, PM	Once-Daily Dose
14 kg to <20 kg	½ tablet (150 mg)	½ tablet (150 mg)	1 tablet (300 mg)
$\geq 20$ kg to <25 kg	½ tablet (150 mg)	1 tablet (300 mg)	1½ tablets (450 mg)
$\geq 25$ kg	1 tablet (300 mg)	1 tablet (300 mg)	2 tablets (600 mg)

#### Child and Adolescent (Weighing $\geq 25$ kg) and Adult Dose:

- ABC 300 mg twice daily or ABC 600 mg once daily

#### [Epzicom] Abacavir/Lamivudine

Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:

- One tablet once daily

#### [Triumeq] Abacavir/Dolutegravir/Lamivudine

Child and Adolescent (Weighing  $\geq 25$  kg) and Adult Dose:

- One tablet once daily
- This FDC tablet can be used in patients who are antiretroviral (ARV)-naïve or ARV-experienced (but integrase strand transfer inhibitor-naïve) and who are not being treated with uridine diphosphate glucuronosyltransferase 1A1 or cytochrome P450 3A inducers.
- The Food and Drug Administration-approved dose for pediatric patients is one tablet once daily for patients weighing  $\geq 40$  kg ([see the Dolutegravir section for more information](#)).

#### [Trizivir] Abacavir/Lamivudine/Zidovudine

Child and Adolescent (Weighing  $\geq 30$  kg) and Adult Dose:

- One tablet twice daily

exacerbation of HBV infection can occur when 3TC is discontinued. Therefore, hepatic function and hepatitis B viral load should be monitored for several months after therapy with 3TC is stopped in patients with HBV.

### Metabolism/Elimination

- ABC is systemically metabolized by alcohol dehydrogenase and glucuronyl transferase.
- The majority of ABC is excreted as metabolites in urine.
- ABC requires a dose adjustment in patients with hepatic insufficiency.
- **Do not use** FDC tablets such as Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets) in patients with impaired hepatic function, because the dose of ABC cannot be adjusted.
- **Do not use** Trizivir, Epzicom, and Triumeq (or the generic equivalents of these FDC tablets) in patients with creatinine clearance <50 mL/min and patients on dialysis, because the dose of 3TC cannot be adjusted.

### Drug Interactions (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- Abacavir (ABC) does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Therefore, it does not cause significant changes in the clearance of agents that are metabolized through these pathways, such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors.
- ABC plasma concentrations can decrease when ABC is used concurrently with the boosted PIs atazanavir/ritonavir, lopinavir/ritonavir, and darunavir/ritonavir.<sup>1-3</sup> The mechanism and the clinical significance of the drug interactions with these PIs are unknown. There are currently no

recommendations for dose adjustments when coadministering ABC and one of these boosted PIs.

- Alcohol exposure (0.7 g per kg ethanol, which is equivalent to five alcoholic drinks) has been shown to interfere with ABC metabolism by affecting the activity of alcohol dehydrogenase and glucuronyl transferase. This interference led to a 41% increase in ABC area under the curve plasma exposure in adult men with HIV who received ABC 600 mg daily.<sup>4</sup>
- ABC oral solution contains sorbitol, which decreased the exposure of lamivudine (3TC) oral solution in adults when the drugs were administered concurrently.<sup>5</sup>

### **Major Toxicities**

- *More common:* Nausea, vomiting, fever, headache, diarrhea, rash, anorexia.
- *Less common (more severe):* Serious and sometimes fatal hypersensitivity reactions (HSRs) that have been observed in approximately 5% of adults and children (the rate varies by race/ethnicity) who were receiving ABC. The HSR to ABC is a multi-organ clinical syndrome that is usually characterized by rash or signs or symptoms in two or more of the following groups:
  - Fever
  - Constitutional symptoms, including malaise, fatigue, or achiness
  - Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhea, or abdominal pain
  - Respiratory signs and symptoms, including dyspnea, cough, or pharyngitis
  - Laboratory and radiologic abnormalities, including elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lymphopenia, and pulmonary infiltrates. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have also been reported. Pancreatitis can occur. HSRs generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of ABC. If an HSR is suspected, ABC **should be stopped immediately and not restarted—hypotension and death may occur upon rechallenge**. The risk of an ABC HSR is associated with the presence of the HLA-B\*5701 allele; the risk is greatly reduced by not using ABC in those who test positive for the HLA-B\*5701 allele.
- *Rare:* Increased levels of liver enzymes, elevated blood glucose levels, elevated triglycerides (see cardiac risk below). Pancreatitis, lactic acidosis, and severe hepatomegaly with steatosis, including fatal cases, have been reported.
- *Rare:* Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome.
- *Rare:* Several observational cohort studies suggest that there is an increased risk of myocardial infarction in adults who are currently using ABC or who have recently used ABC; however, other studies have not substantiated this finding, and there are no **prospective** data on the cardiovascular risks that are associated with ABC use in children. One cohort study of South African adolescents (in which 385 participants had HIV and 63 participants were HIV-negative controls) with a median age of 12 years reported an association between ABC exposure and insulin resistance, which was evaluated using homeostatic model assessment. These findings suggest that the use of ABC may be a cardiovascular risk factor for young people with perinatally acquired HIV.<sup>6</sup>

### **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a [list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

### **Pediatric Use**

#### *Approval*

ABC is approved by the Food and Drug Administration (FDA) for use in children with HIV aged  $\geq 3$  months

as part of the nucleoside reverse transcriptase inhibitor (NRTI) component of antiretroviral therapy (ART). The World Health Organization (WHO), however, recommends using ABC as a component of the NRTI backbone for children weighing  $\geq 3$  kg, starting at 4 weeks of age (see [Dosages of Antiretroviral Drugs from WHO](#)). This recommendation is based on the general principle of using non-thymidine analogues in first-line regimens and thymidine analogues in second-line regimens. This recommendation also takes into account the availability of President's Emergency Plan for AIDS Relief-approved pediatric generic ABC formulations, including coformulations that include 3TC, and the cost of antiretroviral (ARV) drugs in resource-limited settings. No systematic safety assessment has been conducted for using ABC in children weighing  $< 14$  kg.

### *Efficacy*

Both the once-daily and twice-daily doses of ABC have demonstrated durable antiviral efficacy in pediatric clinical trials that is comparable to the efficacy observed for other NRTIs in children.<sup>7-11</sup>

### **Pharmacokinetics**

#### *Pharmacokinetics in Children*

Pharmacokinetic (PK) studies of ABC in children aged  $< 12$  years have demonstrated that metabolic clearance of ABC in adolescents and young adults (aged 13–25 years) is slower than that observed in younger children and approximates clearance seen in older adults.<sup>12</sup>

The PKs of ABC administered once daily in children with HIV aged 3 months through 12 years were evaluated in three crossover, open-label PK trials of twice-daily versus once-daily dosing of ABC and 3TC (PENTA 13 [n = 14], PENTA 15 [n = 18], and ARROW [n = 36]).<sup>4,13-16</sup> The data from these three pediatric trials were used to develop a model for ABC PKs; this model predicted that systemic plasma ABC exposure after once-daily dosing would be equivalent to the exposure seen after twice-daily dosing in infants and children aged  $\leq 12$  years.<sup>13-17</sup> Both these trials and PK modeling have demonstrated that once-daily dosing with either the tablet or the liquid formulation of ABC produces plasma exposures that are comparable to those seen with a twice-daily dosing schedule that uses the same total daily dose of ABC.<sup>18</sup>

### **Dosing**

#### *Dosing and Formulations*

Initially, the recommended dose for pediatric use was ABC 8 mg/kg twice daily, for a total of 16 mg/kg per day. A 2015 FDA review suggested that a total daily dose of ABC 600 mg could be safely used in a person weighing 25 kg (i.e., ABC 24 mg/kg per day, a 50% increase from the previously recommended dose). The weight-band dosing table recommends total daily doses as high as ABC 21.5 mg/kg per day to ABC 22.5 mg/kg per day when treating patients with the tablet formulation.<sup>4</sup> There is no difference in the ABC plasma  $C_{\max}$  and area under the curve for the ABC liquid formulation compared to the tablet formulation.<sup>19</sup> Doses of the liquid ABC formulation are similar to those used for weight-band dosing with tablet formulations and should be considered for use in younger children who are unable to swallow a pill.

In all three ABC dosing pediatric trials described above,<sup>13-16</sup> only children who had low viral loads and who were clinically stable on the twice-daily dose of ABC were eligible to change to once-daily ABC dosing. Efficacy data from a 48-week follow-up in the ARROW trial demonstrated clinical noninferiority of once-daily ABC (n = 336) versus twice-daily ABC (n = 333) in tablet form combined with a once-daily or twice-daily 3TC-based ARV regimen.<sup>9</sup> To date, no clinical trials have been conducted involving children who initiated therapy with once-daily dosing of the ABC liquid formulation. In children who can be treated with pill formulations, initiating therapy with once-daily dosing of ABC at a dose of 16 mg/kg (with a maximum dose of ABC 600 mg) is recommended. However, twice-daily dosing is recommended for infants and young children who initiate therapy with the liquid formulation of ABC. Switching to once-daily dosing with the liquid or pill formulation could be considered in clinically stable children with suppressed viral loads and stable CD4 T lymphocyte cell counts.

## Toxicity

ABC has less of an effect on mitochondrial function than the NRTIs zidovudine, stavudine, or didanosine,<sup>7,8</sup> and less bone and renal toxicity than tenofovir disoproxil fumarate.<sup>20,21</sup>

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